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Reaction of π-Allylnickel Bromide Complexes with Ketones and Aldehydes. Synthesis of α-Methylene-γ-butyrolactones

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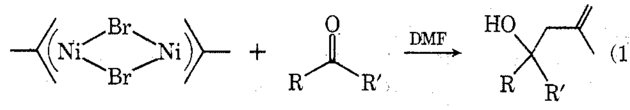
π-Allylnickel bromide complexes react with ketones and aldehydes to produce homoallylic alcohols. α diketones are the most reactive substrates, leading to α-keto homoallylic alcohols. Aldehydes and alicyclic ketones including some steroidal ketones are also reactive, while aliphatic acyclic ketones and α,β-unsaturated ketones react only sluggishly under forcing conditions. With conjugated ketones exclusive 1,2 attack results, even in the presence of added CuI. The reaction of α-(2-carbethoxyallyl)nickel bromide with ketones and aldehydes leads to α-methylene-γ-butyrolactones. Other carbonyl functional groups such as acid chlorides, esters, and amides, as well as nitriles and epoxides, are relatively unreactive. Thus π-allylnickel bromide complexes are less reactive and more selective than the corresponding allylzinc reagents toward carbonyl compounds, and are of potential synthetic utility.

π-Allylnickel halide complexes are becoming increasingly useful as carbon–carbon bond forming reagents for organic synthesis, and have been the subject of two recent reviews.[1,2] They react with a variety of organic halides under mild conditions to replace the halogen with the allyl group.[3] Complexes containing functional groups such as carbethoxy[4] or methoxy[5] in the allyl portion are readily prepared, and react similarly to produce more highly functionalized products. π-Allylnickel bromide complexes react with quinones under very mild (DMF, −50°) conditions to produce allylquinones in what is formally a 1,4 addition of the allyl complex to the quinone.[6] In contrast, other normally reactive carbonyl compounds such as benzaldehyde and cyclopentanone require considerably more vigorous (DMF, 50°) conditions to react, forming homoallylic alcohols, while benzophenone and methyl benzoate are unreactive.[3]

In an attempt to clarify some of the features of the reaction of π-allylnickel halide complexes with quinones, we initiated a general study of the interaction of these complexes with a variety of simple as well as conjugated carbonyl compounds. Our results indicate that these complexes are generally reactive toward ketones and aldehydes to produce fair to excellent yields of homoallylic alcohols under mild conditions. They are significantly *less* reactive than the corresponding allyllithium, -magnesium, or -zinc reagents, and offer a high degree of selectivity among normally quite reactive carbonyl compounds.[7]

Results and Discussion.

A. Reactions of π-2-Methallylnickel Bromide. The general reaction studied is described by eq 1, and the results of this reaction with a wide variety of carbonyl compounds are collected in Table I. The most reactive substrates are α diketones and anthraquinone, which undergo exclusive attack of only one of the carbonyl groups, even in the presence of excess complex, to produce α-keto homoallylic alcohols (**1**, **2**, and **3**) in high yield. Phenyl ketones are more reactive than alkyl ketones as evidenced by the requirement of more severe conditions for 2,3-butanedione. In contrast allylmagnesium and allylzinc complexes frequently attack both carbonyl groups indiscriminately, lead-



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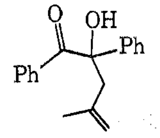
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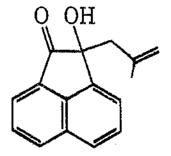
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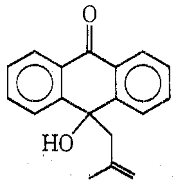
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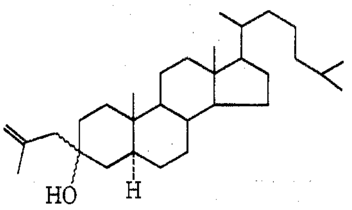
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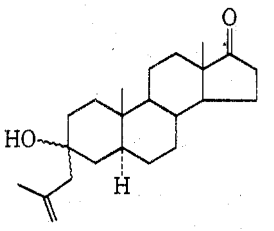
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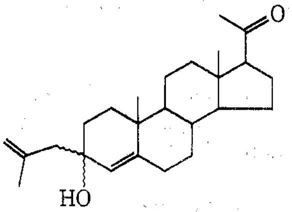
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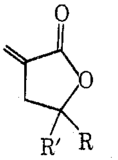

7a, R = Ph; R′ = H
b, R = n-C_6H_{13}; R′ = H
c, R = Ph; R′ = Me
d, R,R′ = $(-CH_2-)_5$
e, R = Ph; R′ = PhCO

Table I
Reaction of π-Allylnickel Bromide Complexes with Ketones and Aldehydes

Ni complex	Registry No.	Substrate	Registry No.	Ratio[a] of allyl/substrate	Time, hr	Temp, °C	Product	Registry No.	Yield, %[b]
2-Methallyl	12300-62-8	Benzil	134-81-6	1	30	25	**1**	53684-09-6	86
2-Methallyl		Acenaphthenequinone	82-86-0	1	48	25	**2**	53684-10-9	84
2-Methallyl		2,3-Butanedione	431-03-8	1.2	24	50	2,4-Dimethyl-4-hydroxyhex-1-en-5-one	40519-29-7	78
2-Methallyl		Anthraquinone	84-65-1	1	48	25	**3**	53684-11-0	92
2-Methallyl		Cyclohexanone	108-94-1	1.7	24	50	1-(2-Methyl-2-propenyl)cyclohexanol	51800-40-9	79
2-Methallyl		5α-Cholestan-3-one	566-88-1	2.2	24	55	**4**(3α-CH) (3β-CH)	53730-91-9 53684-12-1	70[c]
2-Methallyl		5α-Androstane-3,17-dione	846-46-8	2	40	55	**5**(3α-CH) (3β-CH)	53684-13-2 53684-14-3	92[d]
2-Methallyl		2-Cyclohexen-1-one	930-68-7	2.3	96	55	1-(2-Methyl-2-propenyl)cyclohex-2-en-1-ol	5674-03-3	58
2-Methallyl		Progesterone	57-83-0	2.5	24	55	**6**	53684-15-4	77[e]
2-Methallyl		2-Acetonapthone	93-08-3	2.0	48	25	2-Methyl-4-hydroxy-4-(2-naphthyl)pent-1-ene	53684-16-5	80
2-Methallyl		2-Octanone	111-13-7	2.3	96	55	2,4-Dimethyldec-1-en-4-ol	53684-17-6	50
2-Methallyl		*n*-Heptaldehyde	111-71-7	1.2	24	50	2-Methyldec-1-en-4-ol	53684-18-7	71
1,1-Dimethylallyl	32650-02-5	Benzil		1.0	20	25	3,3-Dimethyl-1,2-diphenyl-2-hydroxypent-4-en-1-one 1,2-diphenyl-2-hydroxy-5-methylhex-5-en-1-one	53684-19-8 5623-21-2	28 57
2-Carbethoxyallyl	12288-88-9	Benzaldehyde	100-52-7	2.0	24	25	**7a**	26613-71-8	85
2-Carbethoxyallyl		*n*-Heptaldehyde		2.0	28	25	**7b**	26798-41-4	76
2-Carbethoxyallyl		Acetophenone	98-86-2	2.0	24	55	**7c**	29043-98-9	83
2-Carbethoxyallyl		Cyclohexanone		2.0	24	25	**7d**	52978-85-5	80
2-Carbethoxyallyl		Benzil		2.0	24	55	**7e**	53684-20-1	68
2-Carbethoxyallyl		5α-Cholestan-3-one		2.0	24	55	**8** (3α-O) (3β-O)	53684-21-2 53729-61-5	91[f,g]
2-Carbethoxyallyl		5α-Androstane-3,17-dione		2.0	24	55	**9** (3α-O) (3β-O)	53684-22-3 53684-23-4	76

[a] Since the nickel complexes are dimeric, 1 mol of complex contains 2 mol of allyl ligands. The ratio refers to the molar ratio of allyl groups, not nickel complex, to substrate. [b] Reported yields refer to isolate products purified by layer chromatography or distillation. [c] Since a single epimer was obtained, unequivocal assignment of structure was not possible. [d] The compound is an unseparable 2:1 mixture of 3α and 3β hydroxy isomers from nmr spectra. [e] The yield is based on starting material consumed. About 50% progesterone was recovered. [f] The compound is a 1:1 mixture of 3α and 3β epimers. [g] The yield is based on starting material consumed. About 30% cholestanone was recovered.

ing to disubstitution.[8] Thus, the nickel complex offers a high yield approach to α-keto homoallylic alcohols (as well as to α, β, γ, δ conjugated enones by facile dehydration) without polysubstitution.

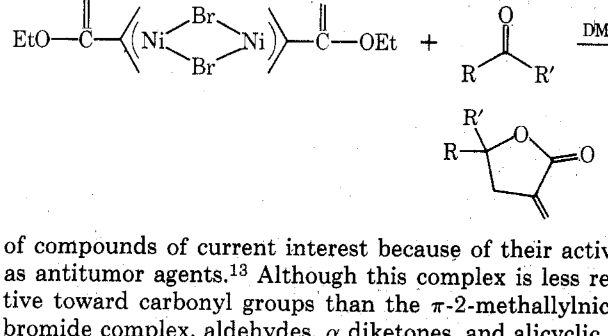
Alicyclic ketones such as cyclopentanone[3] and cyclohexanone also react well, although higher temperatures and excess nickel complex are required to ensure complete reaction. Some steroidal ketones are also reactive, with 5α-cholestan-3-one producing almost entirely (>90%) a single alcohol epimer (**4**) in excellent yield. In contrast, 5α-androstane-3,17-dione, while reacting exclusively at the more reactive[9] 3 keto group, produced a 2:1 mixture of the 3α and 3β hydroxy compounds (**5**). α,β unsaturated ketones are even less reactive, cyclohexenone reacting to only 55% in the presence of a large excess of nickel complex and under conditions sufficiently severe to cause thermal decomposition of the nickel complex. Benzalacetone and chalcone are similarly unreactive, leading to only 40–50% conversion under a variety of conditions. Surprisingly progesterone undergoes attack exclusively at the 3 keto (conjugated) group, while the 20 keto group is inert (**6**), in low (50%) conversion but fair (77%) yield. With α,β unsaturated ketones exclusive 1,2 attack is observed, even in the presence of added cuprous iodide. In contrast, both allylzinc[8] and allylmagnesium compounds are highly reactive toward α,β unsaturated ketones, and organomagnesium compounds add 1,4 to conjugated enones in the presence of added copper salts.[10] Again, π-allylnickel complexes are less reactive and more selective than the corresponding zinc and magnesium complexes.

While phenyl methyl ketones such as 2-acetonaphthone are sufficiently reactive to produce fair yields of homoallylic alcohols under moderate conditions, simple aliphatic ketones, such as 2-octanone, are relatively inert, reacting to only 50% conversion even in the presence of a large excess of nickel complex after 96 hr at 55°. This low reactivity of 2-octanone is demonstrated by the results of the reaction between π-2-methallylnickel bromide and a 1:1 mixture of cyclohexanone and 2-octanone. After 24 hr at 50°, the cyclohexanone had completely reacted, while the 2-octanone remained untouched. Thus the nickel complex was able to discriminate between two substrates of apparently comparable reactivity. Aldehydes are generally reactive, with both benzaldehyde[3] and *n*-heptaldehyde reacting in good yield under moderate conditions.

A number of substrates that readily undergo attack by allylzinc reagents[8] are essentially *unreactive* with π-allylnickel halide complexes. Acetonitrile and benzonitrile are inert, and have been used as solvents for π-allylnickel halide complex reactions.[11] Ethyl benzoate is also unreactive and is recovered unchanged after 165 hr at 55°.[3] Acid chlorides are also surprisingly inert. Both benzoyl chloride and lauryl chloride are recovered unchanged (except for some hydrolysis to the acid during isolation) after 72 hr at 25° in contact with the π-2-methallylnickel complex. Upon heating a DMF solution of benzoyl chloride and π-2-methallylnickel bromide at 50° for 24 hr, the complex decomposed, and a small amount of benzil was recovered along with large amounts of benzoyl chloride and benzoic acid. Finally, cyclohexene oxide failed to react with π-2-methallylnickel bromide even after several hours at 50°, while cyclopentene oxide and styrene oxide reacted to about 30–40%.[11]

B. Reactions of π-1,1-Dimethylallylnickel Bromide. This complex is appreciably less reactive than the π-2-methallylnickel bromide complex. With benzil, one of the most reactive substrates studied, the reaction proceeded smoothly to produce an 85% yield of the homoallylic alcohol. The product is a 2:1 mixture of isomers resulting from attachment at the unsubstituted and the disubstituted terminus of the allyl group.[12] Other substrates such as cyclohexanone, cyclohexenone, and 2-acetonaphthone are unreactive under conditions of sufficient severity to decompose the nickel complex. These results indicate that polyalkylated allylic nickel complexes are likely to lack sufficient reactivity to be of any utility in the synthesis of homoallylic alcohols.

C. Reactions with π-(2-Carbethoxyallyl)nickel Bromide. The reaction of this complex with aldehydes or ketones leads to α-methylene-γ-butyrolactones (eq 2), a class of compounds of current interest because of their activity as antitumor agents.[13] Although this complex is less reactive toward carbonyl groups than the π-2-methallylnickel bromide complex, aldehydes, α diketones, and alicyclic ketones do react to give α-methylene-γ-butyrolactones (7) in high yield. The steroidal ketones 5α-cholestan-3-one and 5α-androstane-3,17-dione react exclusively at the 3 keto (cyclohexanone) position to give a 1:1 mixture of epimeric lactones. Aliphatic ketones such as 2-octanone, and α,β unsaturated ketones such as benzalacetone and cyclohexenone, are essentially unreactive, as are styrene oxide, cyclohexene oxide, and cyclopentene oxide. α-Methylene-γ-butyrolactones can also be made by the reaction of ketones or aldehydes with zinc and α-(bromomethyl)acrylic esters.[14] These allylzinc complexes are considerably more reactive and less selective than the π-allylnickel halide complexes, and react equally well with aliphatic ketones and α,β-unsaturated ketones. Neither method is capable of producing the substitution pattern found in many of the naturally occurring sesquiterpene α-methylene-β-butyrolactones which show antitumor activity.[13a]



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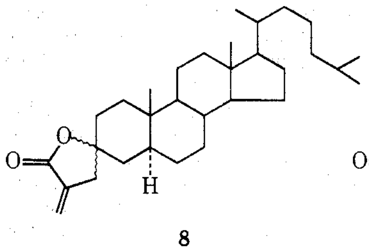
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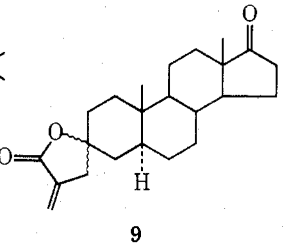
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Conclusions

π-Allylnickel bromide complexes are generally reactive toward ketones and aldehydes to produce homoallylic alcohols. α-Methylene-γ-butyrolactones can be synthesized using the π-(2-carbethoxyallyl)nickel bromide complex. The nickel complexes are considerably less reactive than the corresponding zinc complexes, and considerably more selective. The nickel complexes are inert towards acid halides, nitriles, esters and epoxides, and are even able to discriminate between ketones of differing reactivity. The allylzinc reagents are very easy to make and, in syntheses in which no other reactive functional groups are present in the substrate, they are the reagents of choice. However, if a high degree of selectivity and the ability to discriminate between slightly different carbonyl groups is necessary, π-allylnickel bromide complexes warrant consideration.

Experimental Section

General. All melting points are uncorrected. Infrared (ir) spectra were measured with a Perkin-Elmer Model 337 or Model 267 spectrometer. Nuclear magnetic resonance (nmr) spectra were measured with a Varian Associates Model A-60A or a Jeol JNM-MH-100 nmr spectrometer with TMS internal standard. Mass spectra were measured with an Associated Electronic Industries MS-12 mass spectrometer. Layer chromatography was performed using Brinkman silica gel PF254 analytical and preparative plates, visualized by uv light. Microanalyses were performed by Midwest Microanalytical Laboratory, Indianapolis, Ind. All manipulations of the nickel complexes were carried out under an argon atmosphere.

Materials. DMF was distilled from calcium hydride under reduced pressure and stored under an argon atmosphere. Benzene (Fischer, reagent grade) was used without further purification. Nickel carbonyl was purchased from Matheson in 1-lb lecture bottles. All substrates were commercial materials purified by standard methods.

Preparation of the π-Allylnickel Bromide Complexes. A. π-2-Methallylnickel Bromide. This complex was prepared from 2-methallyl bromide[15] and nickel carbonyl by the method of Semmelhack and Helquist[16] on a 15-g scale with an 85% yield.

B. π-1,1-Dimethylallylnickel Bromide. This complex was prepared from 1,1-dimethylallyl bromide[15,17] and nickel carbonyl by the above method,[16] except the reaction was carried out at reflux rather than 70°.

C. π-(2-Carbethoxyallyl)nickel Bromide. The complex was prepared from 2-carbethoxyallyl bromide[18] and nickel carbonyl by the above method,[16] except the reaction was carried out at 40° rather than 70°. The crude material was dissolved in benzene and filtered under an argon atmosphere. The product was precipitated from the filtrate by addition of petroleum ether, removed by filtration, and dried under vacuum.

General Procedure for the Reaction of π-Allylnickel Bromide Complexes with Ketones and Aldehydes. Reactions were carried out in a 50-ml one-neck flask with a side arm capped with a serum cap, containing a magnetic stirring bar, and fitted with a stopcock. The reaction flask was flushed with argon, and placed in a nitrogen-filled glove bag along with a flask containing complex **1**. The desired amount of 1 (1–2 mmol) was transferred into the reaction flask through the side arm (in the glove bag), the side arm was recapped with the serum cap, and the reaction flask was removed from the glove bag. The complex was dissolved in argon-saturated DMF (10 ml of solvent/mmol complex) giving a deep red solution. Liquid reactants (1.8–3.6 mmol) were directly added to the reaction flask, while solid reactants were dissolved in a minimum amount of DMF and added as solutions. Reactions requiring heat were immersed in an oil bath of the appropriate temperature. Upon completion, the reaction mixture was poured into a separatory funnel containing 50 ml of aqueous 3% HCl and 50 ml of ether, and was thoroughly shaken. The aqueous phase was washed with three 20-ml portions of ether, and the combined ether extracts were washed with three 50-ml portions of water to ensure complete removal of DMF. The organic phase was dried over anhydrous $MgSO_4$, and solvent was removed under vacuum. The crude product was purified by silica gel preparative layer chromatography or distillation.

Reactions with π-2-Methallylnickel Bromide. (a) 1,2-Diphenyl-2-hydroxy-4-methylpent-4-en-2-one (1). The nickel complex (0.25 g, 0.65 mmol) in 12 ml of DMF was added to benzil (0.27 g, 1.29 mmol) and the mixture was stirred at 25° for 35 hr. After routine isolation (Et_2O) and purification by column chromatography (Si gel, eluted with 3:1 hexane–ether) 0.28 g (86%) of a white, crystalline solid (mp 94.5–95.5°) was obtained: ir ($CHCl_3$) 2.85 (OH), 3.27, 3.34, 3.42, 5.95 (conj CO), 6.26, 6.33, 6.70, 6.91, 7.27, 7.60, 7.68, 8.15, 8.40, 8.90, 9.28, 9.75, 9.90, 10.42, 10.60, 11.00, 11.40, 14.30 μ; nmr ($CDCl_3$–TMS) δ 1.55 (d, J = 1.0 Hz, 3 H, vinyl CH_3), AB quartet, δ_A 2.90, δ_B 3.20 (J_{AB} = 14.0 Hz, 2 H, vinyl CH_2; diastereotopic), 4.05 (s, 1 H, OH), 4.63 (m, 1 H, vinyl CH), 4.88 (m, 1 H, vinyl H), 7.2–8.2 (m, 10 H, aromatic H). A portion was recrystallized from ether–trimethylpentane and submitted for analysis.

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.91; H, 6.86.

(b) 1-(2-Methyl-2-propenyl)-1-hydroxy-2-oxoacenaphthene (2). The nickel complex (0.42 g, 1.08 mmol) in 15 ml of DMF was added to the acenaphthene quinone (0.33 g, 1.82 mmol) and the resulting mixture was stirred at 25° for 48 hr. After routine isolation ($CHCl_3$) and purification by recrystallization from ether–trimethylpentane 0.36 g (84%) of a white crystalline solid (mp 110–111°) was obtained: ir ($CHCl_3$) 2.7–3.1 (br, OH), 3.25–3.41 (br, CH), 5.85 (CO), 6.10, 6.15, 6.22, 6.70, 6.80, 7.00, 7.27, 7.45, 7.64, 7.97, 8.50, 9.00, 9.35, 9.92, 10.20, 10.55, 11.10, 11.33, 11.56, 11.95, μ; nmr ($CDCl_3$–TMS) δ 1.41 (s, 3 H, vinyl CH_3), 2.76 (s, 2 H, vinyl CH_2), 3.60 (s, 1 H, OH), 4.58 (m, 2 H, vinyl H), 7.70 (m, 6 H, aromatic H).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.45; H, 5.92.

(c) 2,4-Dimethyl-4-hydroxyhex-1-en-5-one. The nickel complex (0.37 g, 0.96 mmol) in 10 ml of DMF was added to the 2,3-butanedione (0.14 g, 1.65 mmol) and the resulting mixture was stirred at 50° for 24 hr. After routine isolation and purification by evaporative distillation (40° (0.1 mm)) 0.18 g (78%) of a colorless liquid was obtained: ir (neat) 2.87 (br, OH), 3.22, 3.36, 3.42 (CH), 5.83 (C=O), 6.07, 6.88, 7.22, 7.35, 8.55, 8.60, 9.00, 9.90, 10.30, 10.72, 11.20 μ; nmr ($CDCl_3$–TMS) δ 1.38 (s, 3 H, CH_3), 1.72 (d, J = 1 Hz, 3 H, vinyl CH_3), 2.21 (s, 3 H, CH_3CO), 2.44 (s, 2 H, vinyl $-CH_2-$), 3.60 (br, s, 1 H, OH), 4.80 (m, 2 H, vinyl H); mass spectrum parent *m/e* 142.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.32; H, 9.90.

(d) 9-(2-Methyl-2-propenyl)-9-hydroxy-10-oxoanthracene (3). The nickel complex (0.28 g, 0.72 mmol) in 15 ml of DMF was added to the anthraquinone (0.27 g, 1.30 mmol) and the resulting mixture was stirred at 25° for 48 hr. After routine isolation ($CHCl_3$) and purification by recrystallization from chloroform–benzene 0.32 g (92%) of an off-white crystalline solid (mp 174–175°) was obtained: ir ($CHCl_3$) 2.80 (OH), 3.28, 3.32, 3.38, 5.98 (CO), 6.26, 6.87, 7.51, 7.60, 7.79, 7.92, 9.00, 9.80, 10.80, 11.05, 12.60, 14.30 μ; nmr ($CDCl_3$–TMS) δ 0.90 (s, 3 H, vinyl CH_3), 2.64 (s, 2 H, vinyl CH_2), 3.14 (s, 1 H, OH), 3.82 (m, 1 H, vinyl H), 4.50, (m, 1 H, vinyl H), 7.2–8.2 (m, 8 H, aromatic H). The relatively highfield absorption of the methyl allyl group is due to shielding by the ring current effect in the aromatic portion of the molecule.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.72; H, 6.23.

(e) 1-(2-Methyl-2-propenyl)cyclohexanol. Cyclohexanone (0.098 g, 1.00 mmol) was added to the nickel complex (0.33 g, 0.85 mmol) and the resulting mixture was stirred for 24 hr at 50°. After routine isolation and evaporative distillation (80° (0.5 mm)) 0.12 g (70%) of a colorless liquid was obtained: ir (neat) 2.90 (OH), 3.42, 3.52, 6.10, 6.93, 7.30, 7.95, 8.21, 8.50, 8.62, 8.78, 9.22, 9.40, 10.30, 11.20 μ; nmr (CCl_4–TMS) δ 1.48, (br, s, 10 H, ring CH_2), 1.80 (d, J = 1.0 Hz, 3 H, vinyl CH_3), 2.11 (s, 2 H, vinyl CH_2), 4.68 (m, 1 H, vinyl H), 4.84 (m, 1 H, vinyl H). This material was identical in all respects to authentic material prepared by a Reformatsky[7] type reaction.

(f) 5α-Cholestan-3-(2-methyl-2-propenyl)-3-ol (4). A solution of π-2-methallylnickel bromide (0.32 g, 0.83 mmol) in 10 ml of DMF was added to a suspension of 5α-cholestan-3-one (0.29 g, 0.75 mmol) in 10 ml of DMF, and the resulting mixture was stirred at 55° for 40 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 5:1 pentane–ether, three developments, R_f 0.70) 0.23 g (70%) of a white crystalline solid (mp 120–121°) was obtained: ir ($CHCl_3$) 2.72, 2.80, 2.82 (OH), 3.34, 3.38, 3.42, 3.50 (CH), 6.10, 6.82, 6.92, 7.22, 7.40, 8.10, 8.65, 9.00, 9.30, 9.60, 11.00, 12.60, 14.10 μ; nmr ($CDCl_3$–TMS) δ 0.64 (s, 3 H, C_{18} methyl), 0.73 (s, 3 H, C_{19} methyl), 0.85 (d, 6 H, J = 6.0 Hz, C_{25} methyls), 0.86 (d, 3 H, J = 6.0 Hz, C_{20} methyl), 0.98–1.90 (m, 31 H, ring and chain $-CH_2-$, $-CH-$), 1.81 (d, 3 H, J = 1.0 Hz, vinyl CH_3), 2.11 (s, 2 H, vinyl CH_2), 4.80 (m, 2 H, vinyl H).

Anal. Calcd for $C_{31}H_{54}O$: C, 84.09; H, 12.29. Found: C, 84.09; H, 12.22.

The nmr of the crude material showed about 10% of the other hydroxy isomer, but amounts insufficient for characterization were recovered from the chromatography plate.

(g) 5α-Androstan-3-(2-methyl-2-propenyl)-3-hydroxy-17-one (5). A solution of π-2-methallylnickel bromide (0.39 g, 1.01 mmol) in 10 ml of DMF was added to 5α-androstan-3,17-dione (0.29 g, 1.00 mmol) in 10 ml of DMF and the mixture was stirred at 55° for 40 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 3:1 ether–pentane, three developments, R_f 0.80) 0.32 g (92%) of a white crystalline solid (mp 155–158°) was obtained: ir ($CHCl_3$), 2.80 (OH), 3.41, 3.50 (CH), 5.80 (CO of cyclopentanone), 6.10, 6.80, 6.89, 7.11, 7.28, 8.00, 8.92, 9.20, 9.90, 11.08 μ. The nmr spectrum of this material shows it to be a 2:1 mixture of 3α hydroxy and 3β hydroxy isomers. This mixture was not separable in our hands. The spectrum of the mixture is nmr ($CDCl_3$–TMS) δ 0.79 (s, 2 H, C_{19} methyl of 3α hydroxy isomer), 0.88 (s, 4 H, C_{18} methyl of both isomers, and C_{19} methyl of 3β hydroxy isomer), 1.00–2.40 (m, 22 H, ring $-CH_2-$ and $-CH-$), 1.83 (d, 3 H, J = 1.0 Hz, vinyl CH_3), 2.18 (s, 1.33 H vinyl CH_2 of α hydroxy isomer), 2.30 (s, 0.67 H, vinyl CH_2 of β hydroxy isomer), 4.88, (m, 2 H, vinyl H).

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.00; H, 10.62.

The C_{19} methyl absorption of 5α-androstane appears at δ 0.79, while that of 5α-androstan-3β-hydroxy-17-one appears at δ 0.84.[19]

(h) 1-(2-Methyl-2-propenyl)cyclohex-2-en-1-ol. Cyclohexenone (0.096 g, 1.00 mmol) was added to the nickel complex (0.44 g, 1.13 mmol) in 15 ml of DMF and the resulting mixture was stirred for 96 hr at 55°. After routine isolation and purification by evaporative distillation (50° (0.1 mm)) 0.10 g (58%) of a colorless liquid was obtained: ir (neat) 2.90 (OH), 3.25, 3.32, 3.41, 3.50, 3.52 (CH), 6.23, 6.28, 6.62, 6.75, 6.90, 7.20, 7.91, 8.08, 8.56, 9.30, 9.80, 10.40, 11.22, 13.10, 13.50, 14.40 μ; nmr (CCl_4–TMS) δ 1.66 (br s, 4 H, ring CH_2), 1.80 (d, J = 1.0 Hz, 3 H, vinyl CH_3 of allyl), 1.84 (m, 2 H, ring vinyl CH_2), 2.21 (s, 2 H, vinyl CH_2 of allyl), 2.60 (s, 1 H, OH), 4.75 (m, 2 H, vinyl H of allyl), 5.68 (s, 2 H, ring vinyl H). This material was identical in all respects to authentic material prepared by a Reformatsky type reaction.[7]

(i) 4-Pregnen-3-(2-methyl-2-propenyl)-3-hydroxy-20-one (6). A solution of π-2-methallylnickel bromide (0.32 g, 0.83 mmol) in 10 ml of DMF was added to a suspension of progesterone (0.20 g, 0.65 mmol) in 10 ml of DMF and the resulting mixture was stirred at 55° for 48 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 2:1 pentane–ether, R_f 0.60) 62 mg (77% based on starting material consumed) of a white crystalline solid (mp 161–162°) was obtained: ir ($CHCl_3$) 2.70, 2.80, 2.90 (OH), 3.35, 3.37, 3.42, 5.89 (C=O), 6.90, 7.22, 7.30, 7.40, 8.20, 8.90, 9.30, 9.58, 10.80, 11.00, 11.80, 12.60, 14.20, 14.80 μ; nmr ($CDCl_3$–TMS) δ 0.61 (s, 3 H, C_{18} methyl), 1.03 (s, 3 H, C_{19} methyl), 0.9–2.4 (m, 20 H, ring $-CH_2-$ and -CH–), 1.82 (d, 3 H, J = 1.0 Hz, vinyl methyl), 2.10 (s, 3 H, CH_3CO on C_{17}), 2.26 (s, 2 H, vinyl CH_2), 4.82 (m, 2 H, vinyl H on methallyl chain), 5.18 (s, 1 H, C_4 vinyl H).

Anal. Calcd for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34. Found: C, 81.14; H, 10.18.

From spectra this is a single epimer, and unequivocal assignment of structure was not possible. Progesterone (0.14 g) was recovered from R_f 0.40 band, indicating ~50% conversion for this reaction.

(j) 2-Methyl-4-hydroxy-4-(2-naphthyl)pent-1-ene. The nickel complex (0.36 g, 0.93 mmol) in 15 ml of DMF was added to the 2-acetonaphthone (0.16 g, 0.93 mmol) and the resulting mixture was stirred at 25° for 48 hr. After routine isolation and purification by preparative layer chromatography (alumina, 6:1 benzene–ether, two developments, R_f 0.61) 0.18 g (80%) of a colorless oil was obtained: ir (neat) 2.90 (OH), 3.28, 3.36, 3.42 (CH), 6.10, 6.25, 6.66, 6.90, 7.28, 7.45, 7.86, 8.95, 9.20, 9.40, 10.70, 11.20, 11.72, 12.30, 13.40 μ; nmr ($CDCl_3$–TMS) δ 1.40 (d, J = 1.0 Hz, 3 H, vinyl CH_3), 1.52 (s, 3 H, CH_3COH), 2.35 (s, 1 H, OH), AB quartet δ_A 2.40, δ_B 2.69, (J_{AB} = 14.0 Hz, 2 H, vinyl CH_2), 4.73 (m, 2 H, vinyl H), 7.2–7.9 (m, 7 H, aromatic); mass spectrum, parent m/E 226, 208 (P − H_2O), 171 (P − methallyl), 155 (naphthyl − CO^+), 127 (naphthyl$^+$).

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.62; H, 8.02.

(k) 2,4-Dimethyldec-1-en-4-ol. The 2-octanone (0.13 g, 1.00 mmol) was added to the the nickel complex (0.44 g, 1.13 mmol) in 10 ml of DMF and the resulting mixture was stirred at 55° for 96 hr. After routine isolation and purification by evaporative distillation (75° (0.1 mm)) 0.087 g (50%) of a colorless liquid was obtained: ir (neat) 2.90 (OH), 3.39, 3.41, 3.51 (CH), 6.10, 6.86, 7.28, 7.92, 9.00, 9.80, 11.22, 12.40 μ; nmr (CCl_4–TMS) δ 0.95 (m, 3 H, CH_3-C), 1.10 (s, 3 H, CH_3COH), 1.32, (br s, 10 H, $-CH_2-$), 1.82 (s, 3 H, vinyl CH_3) 2.15 (s, 2 H, vinyl CH_2), 4.78 (m, 2 H, vinyl H). A portion was collected from glpc (6 ft × 0.25 in. 10% Carbowax 4000 on Chromosorb P 80/100 AWDMCS, 155°, 2.6 mm) for elemental analysis.

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.41; H, 13.03.

(l) 2-Methyldec-1-en-4-ol. *n*-Heptaldehyde (0.19 g, 1.65 mmol) was added to the nickel complex (0.37 g, 0.96 mmol) and the resulting mixture was stirred at 50° for 24 hr. After routine isolation and evaporative distillation (0.1 mm, 70°) 0.20 g (71%) of a colorless liquid was obtained: ir (neat) 2.93 (OH), 3.22, 3.34, 3.38, 3.48 (CH), 6.06 (C=C), 6.72, 6.83, 7.25, 8.85, 9.20, 9.40, 9.70, 10.33, 11.10 μ; nmr (CCl_4–TMS) δ 0.86 (m, 3 H, CH_3), 1.36 (m, 10 H, $-CH_2-$), 1.78 (s, 3 H, vinyl CH_3), 2.08 (m, 2 H, vinyl $-CH_2-$), 3.60 (m, 1 H, CHOH), 4.80 (m, 2 H, vinyl H); mass spectrum, parent m/e 170. This material was identical to authentic material prepared by a Reformatsky type reaction.[7]

Reaction with π-1,1-Dimethylallylnickel Bromide. (a) With Benzil. The nickel complex (0.24 g, 0.58 mmol) in 15 ml of DMF was added to the benzil (0.23 g, 1.16 mmol) and the resulting mixture was stirred for 20 hr at 25°. After routine isolation and purification by preparative layer chromatography (Si gel, 10:1 pentane–ether, three developments) two major products were obtained.

Compound 1: R_f 0.78; 77 mg (28%) of white solid; ir ($CHCl_3$) 2.85 (OH), 3.26, 3.28, 3.31, 3.38, 3.41, 3.51 (CH), 5.95 (CO), 6.12, 6.29, 6.35, 6.71, 6.77, 6.81, 6.92, 7.08, 7.22, 7.35, 7.52, 7.67, 7.81, 7.90, 8.20, 8.41, 9.18, 9.29, 9.70, 10.00, 10.50, 10.80, 11.80, 12.42, 12.70, 13.50, 14.00, 14.58, 15.30 μ; nmr ($CDCl_3$–TMS) δ 1.09 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 3.05 (s, 1 H, OH), 4.95–5.40 (m, 2 H, C=CH_2), 6.0–6.50 (m, 1 H, =CH), 7.10–7.60 (m, 10 H, aromatic); mass spectrum, parent m/e 280, 263 (P − OH), 175 (P − PhCO), 106 (PhCHO), 78 (PhH).

This material is 3,3-dimethyl-1,2-diphenyl-2-hydroxypent-4-en-1-one from attack on one of the carbonyl groups by the *most* substituted position of the allyl group.

Compound 2: R_f 0.50; 154 mg (57%) of white solid; ir ($CHCl_3$) 2.90 (OH), 3.29, 3.35, 3.42, 3.50 (CH), 5.96 (C=O), 6.25, 6.35, 6.70, 6.90, 7.26, 7.40, 8.10, 8.50, 9.00, 9.36, 9.80, 10.60, 13.20, 14.10, 14.38, 14.40 μ; nmr ($CDCl_3$–TMS) δ 1.41 (s, 3 H, vinyl CH_3), 1.66 (s, 3 H, vinyl CH_3), 3.00 (m, 2 H, vinyl CH_2), 5.12 (m, 1 H, vinyl H), 7.18–7.80 (m, 10 H, aromatic); mass spectrum, parent m/e 280, 263 (P − OH), 212, 175 (P − PhCO), 105 (PhCO+). This material is 1,2-diphenyl-2-hydroxypent-4-en-1-one.

Reactions with π-(2-Carbethoxyallyl)nickel Bromide. Because this complex was less reactive and thermally less stable than the other complexes studied, it was necessary to use excess complex, heat the reaction mixtures to 50°, and separate the desired α-methylene-γ-butyrolactones from the diester resulting from coupling of the allyl ligands.

(a) α-Methylene-γ-phenyl-γ-butyrolactone (7a).[14,20] Benzaldehyde (0.12 g, 1.16 mmol) was added to the nickel complex (0.62 g, 1.16 mmol) in 15 ml of DMF and the resulting mixture was stirred at 25° for 24 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 2:1 pentane–ether, two developments, R_f 0.36) 0.17 g (85%) of a white crystalline solid (mp 55–56°) was obtained: ir ($CHCl_3$) 3.22, 3.25, 3.31, 3.36, 3.40 (CH), 5.64 (lactone C=O), 6.00 (C=C), 6.66, 6.84, 6.96, 7.13, 7.26, 7.68, 7.81, 8.00, 8.50, 8.86, 9.25, 9.77, 10.00, 10.20, 10.55, 10.70, 12.30, 13.25, 14.30 μ; nmr ($CDCl_3$–TMS) δ 2.6–3.7 (m, 2 H, β-CH_2), 5.50 (d of d, J's = 6.6 and 8.0 Hz, 1 H, PhCHO), 5.66 (d of d, J's = 2.6 and 3.0 Hz, 1 H, =CH), 6.23 (d of d, J's = 2.6 and 3.0 Hz, 1 H, =CH), 7.35 (s, 5 H, Ph).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.68; H, 5.94.

(b) α-Methylene-γ-*n*-hexyl-γ-butyrolactone (7b). *n*-Heptaldehyde (0.10 g, 0.90 mmol) was added to the nickel complex (0.47 g, 0.90 mmol) in 15 ml of DMF and the resulting mixture was stirred at 25° for 28 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 2:1 pentane–ether, two developments, R_f 0.58) 0.13 g (76%) of a colorless liquid was obtained: ir (neat) 3.39, 3.41, 3.50 (CH), 5.69 (lactone C=O), 6.01 (C=C), 6.82, 6.92, 7.16, 7.24, 7.82, 7.99, 8.70, 8.95, 9.90, 10.65, 11.38, 12.28, 13.62 μ; nmr ($CDCl_3$–TMS) δ 0.90 (m, 3 H, CH_3), 1.30 (m, 10 H, $-CH_2-$), 2.14–3.37 (m, 2 H, β-CH_2), 4.50 (m, 1 H, γ-CH), 5.62 (d of d, J's = 2.6 and 3.0 Hz, 1 H, C=CH), 6.16 (d of d, J's = 2.6 and 3.0 Hz, 1 H, C=CH); mass spectrum, parent m/e 182.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.63; H, 9.67.

(c) γ-Methyl-α-Methylene-γ-phenyl-γ-butyrolactone (7c). Acetophenone (0.15 g, 1.27 mmol) was added to the nickel complex (0.64 g, 1.27 mmol) in 15 ml of DMF and the mixture was stirred at 55° for 24 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 2:1 pentane–ether, two developments, R_f 0.60) 0.20 g (83%) of a colorless liquid was obtained: ir (neat) 3.23, 3.27, 3.29, 3.36, 3.42 (CH), 5.67 (lactone C=O), 6.00 (C=C), 6.24, 6.67, 6.90, 7.14, 7.24, 7.80, 7.92, 8.25, 8.95, 9.18, 9.49, 10.45, 10.80, 11.20, 12.60, 13.00, 14.30 μ; nmr ($CDCl_3$–TMS) δ 1.68 (s, 3 H, CH_3), 3.13 (d of d, J's = 1.0 and 3.0 Hz, 2 H, β-CH_2), 5.69 (d of d, J's = 1.0 and 3.0 Hz, 1 H, C=CH), 6.18 (d of d, J's = 1.0 and 3.0 Hz, 1 H, C=CH), 7.20 (s, 5 H, Ph); mass spectrum, parent m/e 188.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.35; H, 6.23.

(d) α-Methylene-γ-spirocyclohexane-γ-butyrolactone (7d). Cyclohexanone (0.13 g, 1.30 mmol) was added to the nickel complex (0.69 g, 1.30 mmol) in 15 ml of DMF and the mixture was stirred at 25° for 24 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 2:1 pentane–ether, two developments, R_f 0.55) 0.17 g (80%) of a colorless liquid was obtained: ir (neat) 3.40, 3.50 (CH), 5.67 (lactone C=O), 6.01 (C=C), 6.15, 6.90, 7.16, 7.28, 7.62, 7.84, 7.92, 8.08, 8.35, 8.75, 9.05, 9.65, 10.35, 10.60, 11.20, 11.35, 11.50, 12.25, 13.35 μ; nmr ($CDCl_3$–TMS) δ 1.63 (m, 10 H, cyclohexyl CH_2), 2.74 (t, J = 3.0 Hz, 2 H, β-CH_2), 5.62 (d of t, J's = 2.5 and 0.3 Hz, 1 H, C=CH), 6.17 (d of t, J's = 3.0 and 0.3 Hz, 1 H, C=CH); mass spectrum, parent m/e 166.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.23; H, 8.53.

(e) γ-Benzoyl-α-methylene-γ-phenyl-γ-butyrolactone (7e). The nickel complex (0.60 g, 1.18 mmol) in 20 ml of DMF was added to benzil (0.36 g, 1.72 mmol) and the mixture was heated at 50° for 24 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 7:1 pentane–ether, two developments, R_f 0.30) followed by recrystallization from hexane–ether 0.32 g (68%) of a white crystalline product (mp 64–65°) was obtained: ir ($CHCl_3$) 3.25, 3.28, 3.30, 3.40 (CH), 5.61 (lactone C=O), 5.92 (ketone C=O), 6.25, 6.30, 6.65, 6.89, 7.80, 8.60, 9.25, 9.55, 9.92, 10.50, 11.50, 12.00 μ; nmr ($CDCl_3$–TMS) δ 3.00 (d, J = 16 Hz, 1 H, β-CH_2), 4.24 (d, J = 16 Hz, 1 H, β-CH_2), 5.64 (m, 1 H, vinyl H), 6.24 (m, 1 H, vinyl H), 7.42 (m, 8 H, aromatic), 8.00 (m, 2 H, aromatic).

Anal. Calcd for $C_{18}H_{14}O_3$: C, 76.68; H, 5.07. Found: C, 76.89; H, 5.07.

(f) α-Methylene-γ-(3-spiro-5α-cholestane)-γ-butyrolac-

tone (8). The nickel complex (0.40 g, 0.75 mmol) in 15 ml of DMF was added to 5α-cholestan-3-one (0.30 g, 0.78 mmol) and the resulting mixture was stirred for 24 hr at 25°. After routine isolation the mixture was purified by preparative layer chromatography (Si gel, 10:1 pentane–THF, two developments) and gave three major bands.

Band 1: R_f 0.61; 0.091 g of white solid; unreacted 5α-cholestan-3-one by ir, nmr, and melting point.

Band 2: R_f 0.53; 0.104 g (42%) of white crystalline solid; mp 155–156.5°; ir ($CHCl_3$) 3.41, 3.48 (CH), 5.68 (lactone C=O), 6.01 (C=C), 6.78, 6.82, 6.90, 7.11, 7.20, 7.28, 7.35, 7.49, 7.56, 7.70, 8.05, 8.25, 8.50, 8.60, 8.75, 8.90, 9.10, 9.90, 10.20, 10.55 μ; nmr ($CDCl_3$–TMS) δ 0.65 (s, 3 H, C_{18} methyl), 0.85 (s, 3 H, C_{19} methyl), 0.86 (d, 6 H, $J = 6.0$ Hz, C_{25} methyls), 0.90 (d, 3 H, $J = 6.0$ Hz, C_{20} methyl), 2.79 (t, 2 H, $J = 2.4$ Hz, β-CH_2 in lactone), 5.58 (t, 1 H, $J = 2.4$ Hz, C=CH), 6.20 (t, 1 H, $J = 2.4$ Hz, C=CH). This is the isomer in which the lactone oxygen is β, resulting from attack on the α face, as evidenced by the deshielding of the C_{19} methyl[21] peak as well as the peak of the lactone β-CH_2 group,[5] relative to the other isomer.

Anal. Calcd for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 82.01; H, 11.11.

Band 3: R_f 0.45; 0.123 g (49.5%) of white crystalline solid; mp 209–210°, ir ($CHCl_3$) 3.39, 3.47 (CH), 5.68 (lactone C=O), 6.01 (C=C), 6.80, 6.90, 6.95, 7.11, 7.21, 7.32, 7.69, 7.80, 7.90, 8.08, 8.25, 8.80, 8.91, 9.65, 10.05, 10.30, 10.51, 11.00, 11.10 μ; nmr ($CDCl_3$–TMS) δ 0.65 (s, 3 H, C_{18} methyl), 0.80 (s, 3 H, C_{19} methyl), 0.86 (d, $J = 6.0$ Hz, 6 H, C_{25} methyls), 0.90 (d, $J = 6.0$ Hz, 3 H, C_{20} methyl), 2.67 (t, $J = 2.6$ Hz, 2 H, β-CH_2 in lactone), 5.58 (t, $J = 2.6$ Hz, 1 H, C=CH), 6.20 (t, $J = 2.6$ Hz, 1 H, C=CH). This is isomer in which the lactone oxygen is α, resulting from attack of the β face, as evidenced by the chemical shift of the C_{19} methyl and the lactone β-CH_2 group relative to the other isomer.

Anal. Calcd for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 81.68; H, 11.24.

(g) α-Methylene-γ-(3-spiro-5α-androstan-17-one)-γ-butyrolactone (9). The nickel complex (0.98 g, 1.94 mmol) in 15 ml of DMF was added to 5α-androstane-3,17-dione (0.30 g, 1.10 mmol) and the resulting mixture was heated at 50° for 22 hr. After routine isolation, the desired product was separated from the diester (resulting from coupling of the allyl ligand) by passing through a short column of Si gel. The diester was eluted with 10:1 pentane–THF, and the product lactone eluted with chloroform: yield 0.26 g (76%) of white crystalline solid; ir ($CHCl_3$) 3.40, 3.48, 3.50, 5.67 (lactone CO), 5.75 (cyclopentanone CO), 6.00 (C=C), 6.86, 6.95, 7.10, 7.25, 7.30, 7.59, 7.75, 7.89, 8.05, 8.25, 8.50, 8.78, 9.40, 9.60, 9.71, 9.85, 10.10, 10.51, 11.00, 12.00, 12.20 μ; nmr ($CDCl_3$–TMS) δ 0.83 (s, 6 H, C_{18} and C_{19} CH_3), 1.0–2.0 (m, 20 H, ring CH_2), 2.20 (m, 2 H, CH_2CO), 2.80 (m, 2 H, lactone β-CH_2), 5.65 (m, 1 H, vinyl H), 6.22 (m, 1 H, vinyl H). (Inseparable mixture of epimers.)

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.30; H, 9.12.

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